

SEROTONIN TRANSPORT INHIBITORS

FIELD OF THE INVENTION

The present invention relates to compounds that inhibit 5-hydroxytryptamine reuptake and the use of those compounds on diseases mediated by 5HT receptors.

Compounds that provide such inhibition can be useful, for example, as therapeutic

5 anti-depressants.

BACKGROUND OF THE INVENTION

Serotonin (5-hydroxytryptamine) neurotransmission is regulated and terminated by active transport via the serotonin transporter (SERT). The SERT is
10 member of a large superfamily of sodium/chloride dependent transporters that carry biogenic amines and other biologically active substrates to the interior of cells (Amara SG, Kuhar MJ. 1993. 16:73-93; Blakely RD, et al., 1994. J Exp Biol 196:263-281). Structurally related to dopamine and norepinephrine transporters (Nelson N. 1998. J Neurochem 71:1785-1803), the SERT is the primary site of action of diverse
15 antidepressant drugs, ranging from tricyclics such as imipramine and amitriptyline, to serotonin selective reuptake inhibitors (SSRI's) such as citalopram, fluoxetine and sertraline.

Antidepressant drugs delay the removal of extracellular serotonin from the synapse by blocking serotonin transport, thereby prolonging the duration of serotonin
20 receptor activity. The increased availability of serotonin triggers a cascade of neuroadaptive processes, which produces symptom relief after two to four weeks. Presently known antidepressants also produce certain side effects and may selectively alleviate specific symptoms of depression (Nestler EJ. 1998. Biol Psychiatry 44:526-533). Thus, it is desirable to develop novel antidepressants. The majority of clinically
25 approved drugs to treat depression or obsessive-compulsive disorder are high affinity inhibitors of serotonin and/or norepinephrine transport. Of these transporter inhibitors,

none are tropane analogs, they display low affinity for the dopamine transporter, and all contain an amine nitrogen in their structure.

Over the past decade, a wide array of tropane analogs with high affinity for the monoamine transporters have been synthesized in a program to develop cocaine medications (Madras BK, et al., 1990. *Pharmacol Biochem Behav* 35:949-953; Madras BK, et al., 1996. *Synapse* 24:340-348; Carroll FI, et al., 1992. *J Med Chem* 35:2497-2500; Meltzer PC, et al., 1994. *J Med Chem* 37:2001-2010; Kozikowski AP, et al., 1995. *J Med Chem* 38:3086-3093; Lomenzo SA, et al., 1997. *J Med Chem* 40:4406-4414; Davies HM, et al., 1994. *J Med Chem* 37:1262-1268). The majority of these compounds target the dopamine transporter and have not been considered candidate medications for depression because of stimulant or abuse liability concerns (Reith ME, et al., 1986. *Biochem Pharmacol* 35:1123-1129; Ritz MC, et al., 1987. *Science* 237:1219-1223; Madras BK, et al., 1989. *J Pharmacol Exp Ther* 251:131-141; Bergman J, et al., 1989. *J Pharmacol Exp Ther* 251:150-155). Tropane analogs selective for the serotonin over the dopamine transporter have been reported. (Blough BE, et al., 1996. *J Med Chem* 39:4027-4035; Blough BE, et al., 1997. *J Med Chem* 40:3861-3864; Smith MP, et al., 1998. *J Am Chem Soc* 120:9072-9075; Davies, HM, et al., 1996. *J Med Chem* 39:2554-2558).

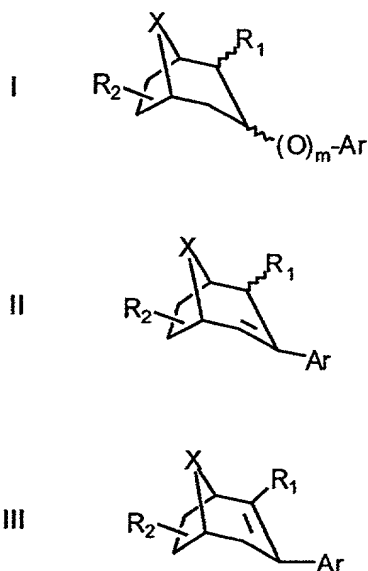
Psychotherapeutics drugs, including antidepressants, all incorporate an amine nitrogen into the structure. In fact, antidepressants presently used have an aromatic ring(s) and an amine nitrogen. Although the aromatic ring is an indispensable component of most drugs acting on biogenic amine receptors or transporters, we previously demonstrated that an amine nitrogen is not necessary for compounds to bind to or block the dopamine transporter (Madras BK, et al., 1996. *Synapse* 24:340-348; Meltzer PC, et al., 1997. *J Med Chem* 40:2661-2673; Meltzer PC, et al., 1999. *Bioorg Med Chem Lett* 9:857-862; Meltzer PC, 2000. *J Med Chem* 43:2982-2991). Biological activity of these compounds was retained if the amine nitrogen was replaced either by an oxygen (oxa) atom or a carbon (carba) atom (Madras BK, et al., 1996. *Synapse* 24:340-348; Madras BK, et al., 1998. *Soc for Neurosci Abst* 24:113.11, 278p; Madras BK, et al., *Addiction Biology* 5:351-359, 2000; Meltzer PC, 2000. *J Med Chem* 43:2982-2991).

It would be desirable to have high affinity non-amines with selectivity for the serotonin transporter and compounds that inhibit the transport of serotonin.

SUMMARY OF THE INVENTION

5 The present invention relates to the discovery that tropane compounds lacking an amine group show surprisingly effective results in treating certain neuropsychiatric disorders related to serotonin transport.

Compounds that are useful as therapeutic agents in the methods of the present invention include non-amine tropane compounds represented by the following general
10 structural formula:



15

wherein:

$R_1 = \text{COOCH}_3, \text{COR}_3, \text{lower alkyl, lower alkenyl, lower alkynyl, CONHR}_4, \text{ or}$
20 $\text{COR}_6;$

$R_2 =$ is a $6\alpha, 6\beta, 7\alpha$ or 7β substituent, which can be selected from H, OH, OR_3 , F, Cl, Br, and NHR_3 ;

$X = \text{CH}_2, \text{CHY, CYY}_1, \text{CO, O, S; SO, SO}_2, \text{ or C=CX}_1\text{Y with the C, O or S}$
atom being a member of the ring;

25 $X_1 = \text{NR}_3, \text{CH}_2, \text{CHY, CYY}_1, \text{CO, O, S; SO, SO}_2, \text{ or NSO}_2\text{R}_3;$

$R_3 = H, (CH_2)_n C_6H_4 Y, C_6H_4 Y, CHCH_2,$ lower alkyl, lower alkenyl or lower alkynyl;

Y and $Y_1 = H, Br, Cl, I, F, OH, OCH_3, CF_3, NO_2, NH_2, CN, NHCOCH_3, N(CH_3)_2, (CH_2)_n CH_3, COCH_3,$ or $C(CH_3)_3$;

5 $R_4 = CH_3, CH_2CH_3,$ or CH_3SO_2 ;

$R_6 =$ morpholinyl or piperidinyl;

$Ar =$ phenyl- $R_5,$ naphthyl- $R_5,$ anthracenyl- $R_5,$ phenanthrenyl- $R_5,$ or diphenylmethoxy- R_5 ;

$R_5 = Br, Cl, I, F, OH, OCH_3, CF_3, NO_2, NH_2, CN, NHCOCH_3, N(CH_3)_2,$
10 $(CH_2)_n CH_3, COCH_3, C(CH_3)_3$ where $n = 0-6, 4-F, 4-Cl, 4-I, 2-F, 2-Cl, 2-I, 3-F, 3-Cl, 3-I, 3,4-diCl, 3,4-diOH, 3,4-diOAc, 3,4-diOCH_3, 3-OH-4-Cl, 3-OH-4-F, 3-Cl-4-OH, 3-F-4-OH,$ lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, $CO(lower\ alkyl),$ or $CO(lower\ alkoxy)$;

$m = 0$ or 1 ; and

15 $n = 0, 1, 2, 3, 4$ or 5 .

Preferred compounds have a SERT/DAT selectivity ratio of at least about 3. Other embodiments have a SERT/DAT selectivity ratio of at least about 8 and other preferably at least about 50.

The invention also relates to compounds shown above that have a potency (K_i),
20 or IC_{50} , at the SERT of less than about 500 nM, preferably less than about 100 nM. In certain preferred embodiments the compounds have a K_i at the SERT less than about 50 nM, preferably less than about 25 nM and more preferably less than about 15 nM.

Especially preferred compounds have a SERT/DAT selectivity ratio of at least about 3 and an IC_{50} at the SERT of less than about 500 nM.

25 The substituents at the 2 and 3 position of the ring can be α - or β -. Thus, the compounds include compounds in the boat and chair conformation. Although R_1 is illustrated in the 2- position, it should be recognized that substitution at the 4-position is also included and the position is dependent on the numbering of the tropane ring. The compounds of the present invention can be racemic, pure *R*-enantiomers, or pure
30 *S*-enantiomers. Thus, the structural formulas illustrated herein are intended to represent each enantiomer and diastereomer of the illustrated compound.

The term "lower alkyl" when used herein designates aliphatic saturated branched or straight chain hydrocarbon monovalent substituents containing from 1 to about 8 carbon atoms such as methyl, ethyl, isopropyl, n-propyl, n-butyl, $(CH_2)_nCH_3$, $C(CH_3)_3$; etc., more preferably 1 to 4 carbons. The term "lower alkoxy" designates
5 lower alkoxy substituents containing from 1 to about 8 carbon atoms such as methoxy, ethoxy, isopropoxy, etc., more preferably 1 to 4 carbon atoms.

The term "lower alkenyl" when used herein designates aliphatic unsaturated branched or straight chain vinyl hydrocarbon substituents containing from 2 to about 8 carbon atoms such as allyl, etc., more preferably 2 to 4 carbons. The term "lower
10 alkynyl" designates lower alkynyl substituents containing from 2 to about 8 carbon atoms, more preferably 2 to 4 carbon atoms such as, for example, propyne, butyne, etc.

The terms substituted lower alkyl, substituted lower alkoxy, substituted lower alkenyl and substituted lower alkynyl, when used herein, include corresponding alkyl,
15 alkoxy, alkenyl or alkynyl groups substituted with halide, hydroxy, carboxylic acid, or carboxamide groups, etc. such as, for example, $-CH_2OH$, $-CH_2CH_2COOH$, $-CH_2CONH_2$, $-OCH_2CH_2OH$, $-OCH_2COOH$, $-OCH_2CH_2CONH_2$, etc. As used herein, the terms lower alkyl, lower alkoxy, lower alkenyl and lower alkynyl are meant to include where practical substituted such groups as described above.

20 When X contains a carbon atom as the ring member, reference to X is sometimes made herein as a carbon group. Thus, when X is a carbon group, as that phrase is used herein, it means that a carbon atom is a ring member at the X position (i.e., the 8- position).

The present invention also relates to therapeutic uses of non-amine tropane
25 analogs. More specifically, the invention relates to methods of treating patients having SERT related disorders, comprising administering to the patient a serotonin reuptake inhibiting amount of a non-amine compound. Such diseases include, but are not limited to, e.g., depression, anxiety, eating disorders and obsessive compulsive disorders and other. The methods specifically include therapies for treating
30 depression.

More specifically, the invention relates to the use of non-amine tropane compounds, as described further below, for the treatment of these diseases. Particularly preferred compounds comprise the compounds shown in Figure 1 and described herein.

5 The present invention provides pharmaceutical therapeutic compositions comprising the compounds formulated in a pharmaceutically acceptable carrier for use in the present methods.

Further, the invention provides a method for inhibiting 5-hydroxytryptamine (Serotonin) reuptake of a monoamine transporter by contacting the monoamine
10 transporter with a 5-hydroxy-tryptamine reuptake inhibiting (5-HT inhibiting) amount of a non-amine tropane compound. Inhibition of 5-hydroxy-tryptamine reuptake of a serotonin transporter in a mammal is provided in accord with the present invention by administering to the mammal a 5-HT inhibiting amount of a non-amine tropane compound in a pharmaceutically acceptable carrier.

15 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the chemical structure of novel amines and novel non-amines, all of which share a tropane backbone.

Figure 2 shows reaction Scheme 1 for the synthesis of 2-carbomethoxy-3-
20 aryl bicyclo(3.2.1)octanes.

Figure 3 shows reaction Scheme 2 for the synthesis of 3-aryl-8-oxabicyclo(3.2.1)octanes.

Figure 4 shows reaction Scheme 3 for the resolution of keto ester.

25 DETAILED DESCRIPTION OF THE INVENTION

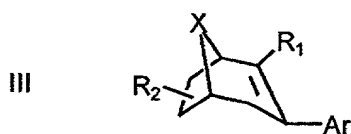
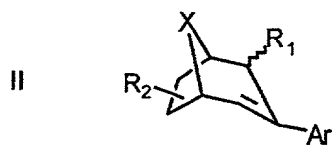
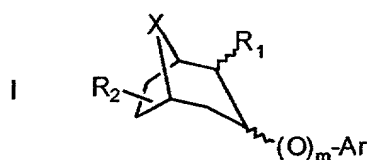
The present invention relates to the use of high affinity serotonin transport inhibitors, designated non-amines, that contain no amine nitrogen in their structure. These tropane analogs, in which the amine nitrogen is replaced by an oxa or carba atom (Madras BK, et al., 1996. Synapse 24:340-348; Meltzer PC, et al., 1997. J Med
30 Chem 40:2661-2673 Meltzer PC, et al., 1997. J Med Chem 40:2661-2673; Meltzer

PC, et al., 1999. Bioorg Med Chem Lett 9:857-862; Meltzer PC, 2000. J Med Chem 43:2982-2991), are generally described in U.S. Patent No. 5,948,933, which issued September 7, 1999.

5 The present invention relates to the use of specific compounds that bind to the SERT to treat neuropsychiatric disorders, wherein the compound is a non-amine and blocks serotonin transport. Certain preferred compounds have a high selectivity for the SERT versus the DAT as described herein.

The compounds used in the methods of the present invention inhibit serotonin uptake and have the following structural formulas:

10 Compounds that are useful as therapeutic agents in the methods of the present invention include compounds represented by the following general structural formula:



wherein:

20 $R_1 = \text{COOCH}_3, \text{COR}_3, \text{lower alkyl, lower alkenyl, lower alkynyl, CONHR}_4, \text{ or } \text{COR}_6;$

$R_2 =$ is a $6\alpha, 6\beta, 7\alpha$ or 7β substituent, which can be selected from H, OH, OR₃, F, Cl, Br, and NHR₃;

$X = \text{CH}_2, \text{CHY, CYY}_1, \text{CO, O, S; SO, SO}_2, \text{ or } \text{C}=\text{CX}_1\text{Y}$ with the C, O or S
25 atom being a member of the ring;

$X_1 = NR_3, CH_2, CHY, CYY_1 CO, O, S; SO, SO_2, \text{ or } NSO_2R_3;$

$R_3 = H, (CH_2)_n C_6H_4Y, C_6H_4Y, CHCH_2, \text{ lower alkyl, lower alkenyl or lower alkynyl};$

$Y \text{ and } Y_1 = H, Br, Cl, I, F, OH, OCH_3, CF_3, NO_2, NH_2, CN, NHCOCH_3,$

5 $N(CH_3)_2, (CH_2)_n CH_3, COCH_3, \text{ or } C(CH_3)_3;$

$R_4 = CH_3, CH_2CH_3, \text{ or } CH_3SO_2;$

$R_6 = \text{morpholinyl or piperidinyl};$

$Ar = \text{phenyl-}R_5, \text{naphthyl-}R_5, \text{anthracenyl-}R_5, \text{phenanthrenyl-}R_5, \text{ or diphenylmethoxy-}R_5;$

10 $R_5 = Br, Cl, I, F, OH, OCH_3, CF_3, NO_2, NH_2, CN, NHCOCH_3, N(CH_3)_2, (CH_2)_n CH_3, COCH_3, C(CH_3)_3 \text{ where } n = 0-6, 4-F, 4-Cl, 4-I, 2-F, 2-Cl, 2-I, 3-F, 3-Cl, 3-I, 3,4-diCl, 3,4-diOH, 3,4-diOAc, 3,4-diOCH_3, 3-OH-4-Cl, 3-OH-4-F, 3-Cl-4-OH, 3-F-4-OH, \text{ lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl, } CO(\text{lower alkyl}), \text{ or } CO(\text{lower alkoxy});$

15 $m = 0 \text{ or } 1; \text{ and}$

$n = 0, 1, 2, 3, 4 \text{ or } 5.$

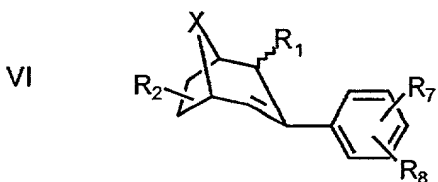
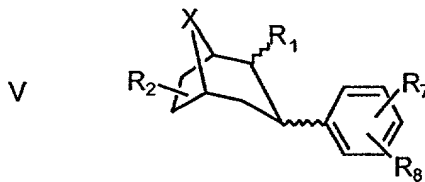
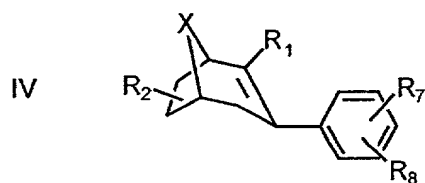
Preferred compounds have a SERT/DAT selectivity ratio of at least about 3. Other embodiments have a SERT/DAT selectivity ratio of at least about 8 and other preferably at least about 50.

20 The invention also relates to compounds shown above that have a potency (K_i), or IC_{50} , at the SERT of less than about 500 nM, preferably less than about 100 nM. In certain preferred embodiments the compounds have a K_i at the SERT more less than about 50 nM, preferably less than about 25 nM and more preferably less than about 15 nM.

25 Especially preferred compounds have a SERT/DAT selectivity ratio of at least about 3 and a potency (K_i) at the SERT of less than about 500 nM.

In another preferred embodiment of the present invention, preferred 8-oxatropanes and 8-carbatropanes include those having alkenyl and alkynyl groups on the 3-aryl ring, particularly of the 2-COOCH₃ tropanes, to enhance potency at the

30 SERT. Particularly preferred examples of such compounds have the following formula:



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where X is an oxygen or a carbon group such as, for example, CH₂, CHY, CYY₁, CO, or C=CX₁Y where X₁, Y and Y₁ are defined above, and R₇ is a lower alkenyl or lower alkynyl group having from about 2 to about 8 carbon atoms. Particularly preferred lower alkenyl and lower alkynyl groups are ethenyl, propenyl, butenyl, propynyl, butynyl and methylpropynyl. R₈ is H or Br, Cl, I, F, OH, OCH₃, CF₃, NO₂, NH₂, CN, NHCOCH₃, N(CH₃)₂, (CH₂)_nCH₃, COCH₃, C(CH₃)₃ where n= 0-6.

The compounds are prepared as racemates and individual enantiomers. These compounds can be prepared either as free bases or as pharmacologically active salts thereof such as hydrochloride, tartrate, sulfate, naphthalene-1,5-disulfonate or the like.

15 In certain preferred compounds, when R₂ is not H, i.e., the compounds are 6 or 7 substituted compounds, the compounds have the 1 S conformation. In other preferred compounds, when R₂ is H, the compounds preferably have the R conformation.

Figure 1 shows the chemical structure of amines and non-amines, all of which share a tropane backbone. The dichlorophenyl substituted non-amines are derived from an amine (aza, O-401) in which the amine nitrogen is replaced with a oxygen (oxa, O-1072) or carbon (carba, O-1391). The naphthyl substituted non-amines are derived from diastereomeric amines (aza, O-1229, O-1228) in which the amine nitrogen is replaced with a carbon (carba, O-1669, O-1670). Compounds O-1585 and

O-1577 are propynylphenyl derivatives. O-1738 and O-1739 are isopropenylphenyl analogs of tropanes.

Examples of preferred compounds for use in the methods of the present invention include, but are not limited to: O-1229: N-methyl-2 β -carbomethoxy-3 β -(2'-naphthyl)-8-azabicyclo(3.2.1)octane; O-1228: N-methyl-2 β -carbomethoxy-3-(2'-naphthyl)-8-azabicyclo(3.2.1)octane; O-1072: 2- β -carbomethoxy-3- β -(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)octane; O-1391: 2- β -carbomethoxy-3- β -(3,4-dichlorophenyl)bicyclo(3.2.1)octane; O-1577: 2 β -carbomethoxy-3 β -(4'-propynylphenyl)-8-oxabicyclo(3.2.1)octane; O-1585: 2 β -carbomethoxy-3 α -(4'-propynylphenyl)-8-oxabicyclo(3.2.1)octane; O-1669: 2 β -carbomethoxy-3 β -(2-naphthyl)-8-bicyclo(3.2.1)octane; O-1670: 2 β -carbomethoxy-3 α -(2-naphthyl)-8-bicyclo(3.2.1)octane; O-1738: 2 β -carbomethoxy-3 α -(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)octane; O-1739: 2 β -carbomethoxy-3 β -(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)octane; O-1809: 2 β -carbomethoxy-3 β -(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)octane. The synthesis of these compounds and other is shown in Figures 2-4 and described below in the Examples.

The compounds described herein provide a broad array of molecules including compounds that bind to the SERT with very high affinity. Selectivity for inhibition of the SERT versus the DAT is another property of tropanes of considerable relevance for development of medications for treating SERT related disorders. Preferred compounds for the present methods exhibit the desired target:non-target (SERT:DAT) specificity. The serotonin transporter is detectable in the striatum, the brain region with the highest density of dopamine neurons and in brain regions surrounding the striatum. It is necessary to determine whether the candidate compound is more potent at the serotonin than the dopamine transporter. If more selective (e.g., >10-fold), the compound will provide effective treatment modality for the SERT. Therefore, a measure of probe affinity of the serotonin transport is conducted by assays paralleling the dopamine transporter assays. As described below, (³H)Citalopram is used to radiolabel binding sites on the serotonin transporter and competition studies are

conducted with the candidate compound at various concentrations in order to generate an IC₅₀ value.

Whether oxa or carba based, non-amines of the present invention bound to (³H)citalopram labeled sites and blocked (³H)serotonin transport in the low nanomolar range. These results are comparable or better than those of some conventional antidepressants. For example, O-1809, is 99-fold more selective for the serotonin transporter over the dopamine transporter.

The non-amines had varying affinities and serotonin:dopamine transporter selectivities, as measured in monkey brain tissue (Table 2). As described above, preferred compounds for use in the methods of the present invention have a SERT/DAT selectivity ratio of at least about 3. Other embodiments have a SERT/DAT selectivity ratio of at least about 8 and other preferably at least about 50. Examples of preferred serotonin transporter-selective non-amines include O-1809, O-1739, O-1577, O-1738 and O-1585.

Affinity, i.e., binding to the SERT, is another characteristic that is useful for selecting useful compounds. The oxa (O-1072) or carba (O-1391) analogs of O-401, a high affinity amine that is relatively non-selective for the dopamine over the serotonin transporter, displayed similar high affinity and non-selective binding to the dopamine and serotonin transporters. The compounds of the present invention have an affinity, also known as potency, IC₅₀ or K_i, at the SERT of less than about 500 nM, preferably less than about 50 nM. In certain preferred embodiments the compounds have a K_i at the SERT more preferably less than about 25 nM and more preferably less than about 15 nM.

For example, the non-amines O-1072, O-1391, O-1809, O-1669, O-1739 blocked (³H)serotonin transport in the low nanomolar range, comparable to the potencies of the conventional amine antidepressants, imipramine, fluoxetine and amitriptyline (see Tables 1-4). Amine antidepressants displayed lower potencies for blocking serotonin transport than for binding to (³H)citalopram labeled sites. Initially reported in 1997 (Owens MJ, et al., 1997. J Pharmacol Exp Ther 283:1305-1322), this discrepancy between drug binding potencies and blockade of serotonin transport was not observed if (¹²⁵I)RTI-55 was used to label the serotonin transporter (Eshleman AJ,

et al., 1999. J Pharmacol Exp Ther 289:877-885), but was even more prominent with (³H)paroxetine as a probe for the serotonin transporter (Kuhar MJ, et al., 1999. Drug Alcohol Depend 56:9-15). The potencies of non-amines for blocking the serotonin transporter are comparable to conventional and widely used amine-based

5 antidepressants.

Using the combination of selectivity (SERT/DAT ratio) and potency (IC₅₀) information for these compounds, one of ordinary skill in the art can readily select the appropriate compound for the desired application, e.g., treatment of SERT related disorders.

10 Substituents on the aromatic ring of non-amines enhanced SERT affinities by 10 to 1,000-fold. The increases were greater than those observed with corresponding monoamines. Certain preferred compounds for use in the present invention are non-amines with substituted aromatic rings at the 3 position.

The compounds and pharmaceutical preparations of the present invention can
15 be used to inhibit the serotonin reuptake by the serotonin transporter. The pharmaceutical compositions, preferably comprise the compounds of the present invention in a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those skilled in the art. An exemplary pharmaceutical composition is a therapeutically effective amount of a compound of the invention optionally included
20 in a pharmaceutically-acceptable and compatible carrier. The term "pharmaceutically-acceptable and compatible carrier" as used herein, and described more fully below, refers to e.g., one or more compatible solid or liquid filler diluents or encapsulating substances that are suitable for administration to a human or other animal. The route of administration can be varied but is principally selected from intravenous, nasal and
25 oral routes. For parenteral administration, e.g., it will typically be injected in a sterile aqueous or non-aqueous solution, suspension or emulsion in association with a pharmaceutically-acceptable parenteral carrier such as physiological saline.

The term "therapeutically-effective amount" is that amount of the present pharmaceutical compositions which produces a desired result or exerts a desired
30 influence on the particular condition being treated. Various concentrations may be used in preparing compositions incorporating the same ingredient to provide for

variations in the age of the patient to be treated, the severity of the condition, the duration of the treatment and the mode of administration. An effective dose of the compound is administered to a patient based on IC_{50} values determined in vitro. The route of administration can be varied but is principally selected from intravenous, nasal and oral routes. The effective dose can vary depending upon the mode of administration as is well known in the art.

The term "compatible", as used herein, means that the components of the pharmaceutical compositions are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction that would substantially impair the desired pharmaceutical efficacy.

The dose of the pharmaceutical compositions of the invention will vary depending on the subject and upon particular route of administration used. The pharmaceutical compositions can also be administered to a subject according to a variety of well-characterized protocols. In a preferred embodiment, the pharmaceutical composition is a liquid composition in pyrogen-free, sterilized container or vial. The container can be unit dose or multidose.

This invention will be illustrated further by the following examples. These examples are not intended to limit the scope of the claimed invention in any manner. The Examples provide suitable methods for preparing compounds of the present invention. However, those skilled in the art may make compounds of the present invention by any other suitable means. As is well known to those skilled in the art, other substituents can be provided for the illustrated compounds by suitable modification of the reactants.

25 **EXAMPLES**

Materials

The following drugs were obtained from the sources listed: (-)cocaine hydrochloride (National Institute on Drug Abuse, Bethesda, MD); mazindol base (Sandoz Inc., East Hanover, NJ); citalopram hydrobromide and talsupram hydrochloride (Lundbeck A/S, Copenhagen, Denmark); dopamine hydrochloride, (-)-norepinephrine bitartrate and serotonin creatinine sulfate (Sigma Chemical Co., St. Louis, MO); RTI-55 methyl

ester tartrate (F. Ivy Carroll, Research Triangle Institute, Research Triangle Park, NC); imipramine (Ciba Pharmaceuticals, Summit, NJ); sertraline (McNeil Pharmaceutical, Raritan, NJ); fluoxetine hydrochloride (Eli Lilly, Indianapolis, IN and Sigma/Research Biochemicals, Natick, MA); amitriptyline and desipramine (Merck Sharp and Dohme Ltd., Rahway, NJ). Amine and non-amine drugs, designated with the prefix O-, were synthesized by Organix Inc., (Woburn, MA) in accordance with the methods described in Patent No. 5,948,933, Meltzer, et al, J. Med. Chem. 40, 2661-2673, 1997 and Reference: Meltzer et al, J. Med. Chem. 43, 2982-2991, 2000. Examples of preferred structures are shown in Figure 1.

CHEMICAL SYNTHESIS:

A. SYNTHESIS OF 2-CARBOMETHOXY-3-ARYLBICYCLO (3.2.1)OCTANES.

Scheme 1 (Figure 2) shows the Synthesis of 2-carbomethoxy-3-arylbicyclo (3.2.1)octanes. All compounds are racemates (1*R*/1*S*). NMR spectra were recorded in CDCl₃ on a JEOL 300 NMR spectrometer operating at 300.53 MHz for ¹H, and 75.58 MHz for ¹³C. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Thin layer chromatography (TLC) was carried out on Baker Si250F plates. Visualization was accomplished with either UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40mM. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. All reactions were conducted under an inert (N₂) atmosphere. (³H)WIN 35,428 (2β-carbomethoxy-3 β-(4-fluorophenyl)-N-(³H)methyltropane, 79.4-87.0 Ci/mmol) and (³H)citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). A Beckman 1801 scintillation counter was used for scintillation spectrometry. 0.1% Bovine serum albumin was purchased from Sigma Chemicals. (*R*)-(-)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse (NIDA).

2-Carbomethoxy-bicyclo(3.2.1)octan-3-one (3).

To bicyclo(3.2.1)octan-3-one, **2**²⁷ (6.42 g, 51.7 mmol) in THF (75 mL), lithium diisopropyl amide (31 mL, 62 mmol) in THF (125 mL) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 1 h and methyl cyanoformate (4.9 mL, 62 mmol) was added. The cooling bath was removed and the reaction allowed to warm to room temperature. After stirring for 2 h, saturated aqueous NaCl (32 mL) was added and about half of THF removed on a rotary evaporator. The remaining solvent was extracted with ether (3 x 150 mL) and the dried (Na₂SO₄) ether layer concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 7.85 g (83%) of **3** as a colorless oil: *R*_f 0.56 (10% EtOAc/hexanes); ¹H-NMR (75:15:10 mixture of 2-en-3-ol, 2-α, and 2-β-carbomethoxy-3-keto tautomers) δ 11.87 (s, 1H); 3.73 (s, 3H), 3.70 (s, 0.6H), 3.69 (s, 0.4H), 3.42 (m, 0.2H), 3.19 (m, 0.13H), 2.93 (m, 1H), 2.81 (m, 0.13H), 2.71 (m, 0.2H), 2.65 (ddd, 0.13H, *J* = 18, 4, 2 Hz), 2.55 (ddd, 1.2H, *J* = 18, 4, 2 Hz), 2.41 (m, 1H), 2.34 (m, 0.2H), 2.29 (m, 0.13H), 2.03 (dd, 1H, *J* = 18, 2 Hz), 1.65-1.95 (m, 4.4H), 1.30-1.55 (m, 3.6H). ¹³C-NMR (only the signals corresponding to the 2-en-3-ol tautomer are reported) δ 172.00, 171.19, 105.38, 51.33, 40.19, 35.92, 35.58, 32.91 (2C), 29.90.

2-Carbomethoxy-3-(((trifluoromethyl)sulfonyl)oxy)-bicyclo(3.2.1)-2-octene (4).

To 2-carbomethoxy-bicyclo(3.2.1)octan-3-one, **3** (6.0 g, 3.29 mmol) in THF (120 mL), sodium bis(trimethylsilyl) amide (1.0M solution in THF, 49.4 mL) was added dropwise at -78 °C. After stirring for 30 min, N-phenyltrifluoromethane sulfonimide (17.6 g, 4.94 mmol) was added in one portion. After 10 min, the cooling bath was removed and the reaction mixture stirred overnight. Water (100 mL) was added to the reaction mixture and extracted with diethyl ether (3 x 150 mL). The dried (Na₂SO₄) ether layers were concentrated to dryness on a rotary evaporator. The residue was purified by flash chromatography (eluent: 20% EtOAc/hexanes) to afford 7.8 g (75%) of **4** as a colorless oil: *R*_f 0.56 (20% EtOAc/hexanes); ¹H-NMR δ 3.79 (s,

3H), 3.10 (m, 1H), 2.71 (dd, 1H, $J = 18, 5$ Hz), 2.52 (m, 1H), 2.17 (dd, 1H, $J = 18, 2$ Hz), 1.75-2.05 (m, 3H), 1.45-1.70 (m, 3H). ^{13}C -NMR δ 164.44, 151.02, 129.04, 118.23 (q, $J = 320$ Hz), 52.05, 39.68 (d, $J = 1$ Hz), 36.61, 35.34, 34.51, 33.31, 30.01.

5 **2-Carbomethoxy-3-(3,4-dichlorophenyl)-bicyclo(3.2.1)-2-octene (5a).**

- 2-Carbomethoxy-3-(((trifluoromethyl)sulfonyl)oxy)-bicyclo(3.2.1)-2-octene, **4** (2.0 g, 63.6 mmol), 3, 4-dichlorophenyl boronic acid (1.58 g, 82.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.29 g, 0.32 mmol), Na_2CO_3 (2M solution, 6.4 mL) and diethoxymethane (32 mL) were combined and refluxed at 95 °C for 4h.
- 10 Tris(dibenzylideneacetone) dipalladium(0) (1.45 g) was then added in five equal portions at 4h interval. The reaction mixture was cooled to room temperature, filtered through Celite, and washed with ether (200 mL). The ether solution was then washed with saturated aqueous NaCl (100 mL). The dried (Na_2SO_4) ether layer was removed on a rotary evaporator. The residue was purified by flash chromatography (eluent:
- 15 10% EtOAc/hexanes) to afford 1.38 g (69%) of **5a** as a colorless oil: R_f 0.50 (10% EtOAc/hexanes); ^1H -NMR δ 7.34 (d, 1H, $J = 8$ Hz), 7.17 (d, 1H, $J = 2$ Hz), 6.90 (dd, 1H, $J = 8, 2$ Hz) 3.49 (s, 3H), 3.00 (bt, 1H, $J = 5$ Hz), 2.64 (ddd, 1H, $J = 19, 4, 2$ Hz), 2.44 (m, 1H), 2.14 (dd, 1H, $J = 19, 1$ Hz), 1.75-2.05 (m, 3H), 1.45-1.70 (m, 3H). ^{13}C -NMR δ 168.54, 142.60, 142.13, 135.55, 132.07, 130.95, 130.00, 128.80, 126.45,
- 20 51.48, 44.52, 37.13, 35.65, 34.86, 33.24, 30.76. Anal. ($\text{C}_{16}\text{H}_{16}\text{O}_2\text{Cl}_2$) C, H, Cl.

2-Carbomethoxy-3-naphthyl-bicyclo(3.2.1)-2-octene (5b).

- 2-Carbomethoxy-3-(((trifluoromethyl)sulfonyl)oxy)-bicyclo(3.2.1)-2-octene, **4** (0.50 g, 1.60 mmol), 2-naphthaleneboronic acid (0.36 g, 2.08 mmol),
- 25 tris(dibenzylideneacetone) dipalladium(0) (0.07 g, 0.08 mmol) Na_2CO_3 (2M solution, 1.6 mL) and diethoxymethane (8 mL) were combined and refluxed at 95 °C overnight. The reaction mixture was cooled to room temperature, filtered through Celite and washed with ether (100 mL). The ether solution was then extracted with saturated aqueous NaCl (50 mL). The dried (Na_2SO_4) ether layer was removed on a rotary
- 30 evaporator. The residue was purified by flash chromatography (eluent: 10%

EtOAc/hexanes) to afford 0.25 g (54%) of **5b** as a colorless oil: *R_f* 0.41 (10% EtOAc/hexanes); ¹H-NMR δ 7.83 (m, 3H), 7.62 (d, 1H, *J* = 1 Hz), 7.48 (m, 2H), 7.28 (dd, 1H, *J* = 9, 2 Hz), 3.44 (s, 3H), 3.14 (bt, 1H, *J* = 5 Hz), 2.84 (ddd, 1H, *J* = 19, 4, 1 Hz), 2.53 (m, 1H), 2.38 (bd, 1H, *J* = 19 Hz), 1.80-2.20 (m, 4H), 1.60-1.75 (m, 2H). ¹³C-NMR δ 169.17, 143.83, 139.85, 134.55, 133.04, 132.33, 127.76, 127.47, 127.21, 125.83, 125.54 (2), 124.86, 51.04, 44.35, 37.16, 35.54, 34.82, 33.21, 30.60. Anal. (C₂₀H₂₀O₂) C, H.

2-Carbomethoxy-3-(4-fluorophenyl)-bicyclo(3.2.1)-2-octene (**5c**).

Compound **5c** was obtained from with 4-fluorophenylboronic acid as described for **5a**: A colorless oil was obtained (73%): *R_f* 0.5 (10% EtOAc/hexanes); ¹H-NMR δ 6.95-7.10 (m, 4H), 3.46 (s, 3H), 3.00 (t, 1H, *J* = 5 Hz), 2.67 (dd, 1H, *J* = 19, 4 Hz), 2.46 (m, 1H), 2.20 (bd, 1H, *J* = 19 Hz), 1.50-2.05 (m, 6H). ¹³C-NMR δ 169.10, 161.86 (d, *J* = 245 Hz), 143.05, 138.32, 134.69, 128.30 (d, *J* = 8 Hz), 114.81 (d, *J* = 21 Hz), 51.18, 44.53, 37.15, 35.55, 34.86, 33.21, 30.65. Anal. (C₁₆H₁₇O₂F) C, H.

2-Carbomethoxy-3-phenyl-bicyclo(3.2.1)-2-octene (**5d**).

Compound **5d** was prepared from with phenylboronic acid as described for **5a**: A colorless oil was obtained (75%): *R_f* 0.5 (10% EtOAc/hexanes); ¹H-NMR δ 7.27 (m, 3H), 7.08 (m, 2H), 3.43 (s, 3H), 3.00 (bt, 1H, *J* = 5), 2.70 (ddd, 1H, *J* = 19, 4, 1 Hz), 2.46 (m, 1H), 2.23 (bd, 1H, *J* = 19 Hz) 1.80-2.05 (m, 3H), 1.73 (d, 1H, *J* = 11 Hz), 1.50-1.65 (m, 2H). ¹³C-NMR δ 169.31, 144.03, 142.46, 134.28, 127.88, 126.95, 126.61, 51.11, 44.37, 37.17, 35.60, 34.90, 33.26, 30.66. Anal. (C₁₆H₁₈O₂) C, H.

2(α, β)-Carbomethoxy-3(α, β)-(4-fluorophenyl)bicyclo(3.2.1)octane (**6c**).

Magnesium (47 mg, 1.90 mmol) was added into 2-carbomethoxy-3-(4-fluorophenyl)-bicyclo(3.2.1)-2-octene, **5c** (50 mg, 0.19 mmol) in methanol (2 mL). After 1 h, additional magnesium (47 mg, 1.90 mmol) was added and stirred for 4 h. 1N HCl (4 mL) was added dropwise and stirred for 1 h. The reaction mixture was

extracted with ether (3 x 20 mL) dried over Na₂SO₄ and the ether layer removed on a rotary evaporator. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 42 mg (84%) of **6c** as a colorless oil: *R*_f 0.42 (10% EtOAc/hexanes). Anal. (C₁₆H₁₉FO₂) C, H.

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2(α, β)-Carbomethoxy-3(α, β)-phenylbicyclo(3.2.1)octane (6d).

Compound **6d** was prepared from **5d** with magnesium as described for **6c**. A colorless oil was obtained (48%): *R*_f 0.42 (10% EtOAc/hexanes); Anal. (C₁₆H₂₀O₂) C, H.

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2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-bicyclo(3.2.1)octane (7a),

2α-Carbomethoxy-3β-(3,4-dichlorophenyl)-bicyclo(3.2.1)octane (8a),

2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-bicyclo(3.2.1)octane (9a), and

2α-Carbomethoxy-3α-(3,4-dichlorophenyl)-bicyclo(3.2.1)octane (10a).

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To 2-carbomethoxy-3-(3,4-dichlorophenyl)-bicyclo(3.2.1)-2-octene, **5a** (1.38 g, 4.43 mmol) in methanol (50 mL) at -78 °C, SmI₂ (0.1M in THF, 237 mL) was added dropwise via an addition funnel. After completing the addition, the green mixture was stirred for 4h at -78 °C and quenched with TFA (20 mL) in ether (60 mL). H₂O (50 mL) was added and extracted with ether (3 x 200 mL). The dried

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(Na₂SO₄) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 20% EtOAc/hexanes) to afford a mixture of isomers **6a** (1 g, 72%). The isomers were separated by gravity column chromatography (eluent: 10-50% toluene/hexanes) to afford 65 mg of **7a** as a white solid (mp 81.1-81.4 °C), 280mg of **8a** as a white solid (mp 65.3-65.6 °C), 58 mg of **9a** as a white solid (mp

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82.8-83.3 °C) and 42mg of **10a** as a white solid (mp 83.2-83.8 °C). **7a**: ¹H-NMR δ 7.31 (d, 1H, *J* = 2 Hz), 7.30 (d, 1H, *J* = 8 Hz), 7.08 (ddd, 1H, *J* = 8, 2, 1 Hz), 3.44 (s, 3H), 2.98 (ddd, 1H, *J* = 13, 6, 6 Hz), 2.84 (dd, 1H, *J* = 6, 6 Hz), 2.53 (m, 1H), 2.42 (m, 1H), 2.31 (ddd, 1H, *J* = 13, 13, 2 Hz), 1.45-2.00 (m, 5H), 1.85 (bd, 1H, *J* = 12 Hz), 1.28 (ddd, 1H, *J* = 12, 6, 6 Hz). ¹³C-NMR δ 173.24, 144.03, 131.86, 129.77, 129.75, 129.63, 126.95, 52.15, 51.05, 38.37, 35.91, 34.54, 33.24, 32.95, 29.59, 28.03. Anal.

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(C₁₆H₁₈Cl₂O₂) C, H, Cl. **8a**: ¹H-NMR δ 7.31 (d, 1H, *J* = 8 Hz), 7.30 (d, 1H, *J* = 2 Hz) 7.06 (dd, 1H, *J* = 8, 2 Hz), 3.51 (s, 3H), 3.10 (ddd, 1H, *J* = 12, 12, 6 Hz), 2.66 (dd, 1H, *J* = 12, 2 Hz), 2.48 (m, 1H), 2.32 (m, 1H), 1.87 (m, 1H), 1.45-1.80 (m, 7H). ¹³C-NMR δ 173.94, 144.94, 132.11, 130.18, 129.95, 129.61, 127.18, 52.82, 51.40, 40.83, 39.26, 38.70, 38.28, 34.95, 28.60, 25.14. Anal. (C₁₆H₁₈Cl₂O₂) C, H, Cl. **9a**: ¹H-NMR 7.30 (d, 1H, *J* = 8 Hz), 7.25 (d, 1H, *J* = 2 Hz) 7.01 (dd, 1H, *J* = 8, 2 Hz), 3.54 (s, 3H), 3.03 (ddd, 1H, *J* = 12, 12, 8 Hz), 2.36 (d, 1H, *J* = 12 Hz), 2.30-2.40 (m, 2H), 2.24 (ddd, 1H, *J* = 12, 8, 8 Hz), 1.94 (m, 1H), 1.92 (bd, 1H, *J* = 12 Hz), 1.74 (m, 1H), 1.56 (m, 1H), 1.44 (m, 1H), 1.20 (dd, 1H, *J* = 12, 12 Hz), 1.10 (ddd, 1H, *J* = 12, 4, 4 Hz). ¹³C-NMR δ 175.68, 145.19, 132.14, 130.18, 130.05, 129.70, 127.30, 55.93, 51.60, 38.92, 36.99, 36.70, 33.44, 32.89, 31.76, 29.83. Anal. (C₁₆H₁₈Cl₂O₂) C, H, Cl. **10a**: ¹H-NMR δ 7.31 (dd, 1H, *J* = 2, 1 Hz), 7.28 (d, 1H, *J* = 8 Hz), 7.07 (ddd, 1H, *J* = 8, 2, 1 Hz), 3.45 (s, 3H), 3.31 (dd, 1H, *J* = 6, 6 Hz), 3.11 (ddd, 1H, *J* = 12, 6, 6 Hz), 2.64 (m, 1H), 2.37 (m, 1H), 2.16 (ddd, 1H, *J* = 12, 6, 6 Hz), 1.95 (bdd, 1H, *J* = 12, 12 Hz), 1.82 (bd, 1H, *J* = 12 Hz), 1.73 (m, 1H), 1.50-1.65 (m, 2H), 1.42 (m, 1H), 1.28 (ddd, 1H, *J* = 12, 4, 4 Hz). ¹³C-NMR δ 173.70, 144.18, 131.76, 129.88, 129.61, 129.48, 127.04, 50.89, 50.11, 35.23, 34.49, 34.47, 33.54, 32.31, 32.02, 27.02. Anal. (C₁₆H₁₈Cl₂O₂) C, H, Cl.

2β-Carbomethoxy-3β-naphthyl-bicyclo(3.2.1)octane (7b),
2α-Carbomethoxy-3β-naphthyl-bicyclo(3.2.1)octane (8b),
2β-Carbomethoxy-3α-naphthyl-bicyclo(3.2.1)octane (9b) and
2α-Carbomethoxy-3α-naphthyl-bicyclo(3.2.1)octane (10b).

To 2-carbomethoxy-3-naphthyl-bicyclo (3.2.1)-2-octene, **5b** (0.75 g, 2.57 mmol) in methanol (30 mL) at -78°C, SmI₂ (0.1M in THF, 200 mL) was added dropwise via an addition funnel. After completing the addition, the green mixture was stirred for 4h at -78 °C and quenched with TFA (10 mL) in ether (30 mL). H₂O (25 mL) was added and extracted with ether (3 x 100 mL). The dried (Na₂SO₄) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford a mixture of isomers, **6b** (0.48 g, 64%). The isomers were separated by gravity column chromatography (eluent: 40-80%

toluene/hexanes) to afford 20 mg of **7b** as a white solid (mp 78.8-79.1 °C), 30 mg of **8b** as a white solid (mp 71.3-71.7 °C), 50 mg of **9b** as a white solid (mp 71.1-71.4 °C), and **10b** as a white solid (mp 91.1-91.3 °C). **7b**: ¹H-NMR δ 7.77 (m, 2H), 7.73 (d, 1H, *J* = 9 Hz), 7.68 (bs, 1H), 7.41 (m, 3H), 3.32 (s, 3H), 3.22 (ddd, 1H, *J* = 12, 6, 6 Hz), 3.00 (dd, 1H, *J* = 6, 4 Hz), 2.56 (m, 1H), 2.54 (m, 1H), 2.48 (m, 1H), 2.00 (bd, 1H, *J* = 12 Hz), 1.92 (m, 1H), 1.55-1.85 (m, 4H), 1.32 (ddd, 1H, *J* = 12, 6, 6 Hz). ¹³C-NMR δ 173.76, 141.10, 133.49, 132.16, 127.90, 127.52, 127.42, 126.45, 125.98, 125.75, 125.26, 52.55, 50.96, 38.60, 36.83, 34.85, 33.58, 33.16, 29.92, 28.29. Anal. (C₂₀H₂₂O₂) C, H. **8b**: ¹H-NMR δ 7.76(m, 3H), 7.66 (bd, 1H, *J* = 2 Hz), 7.40 (m, 3H), 3.43 (s, 3H), 3.31 (ddd, 1H, *J* = 12, 12, 6 Hz), 2.88 (dd, 1H, *J* = 12, 2 Hz), 2.51 (m, 1H), 2.35(m, 1H), 2.00 (m, 1H), 1.50-1.85 (m, 7H). ¹³C-NMR δ 174.56, 142.13, 133.66, 132.41, 127.99, 127.77, 127.61, 126.44, 126.12, 125.85, 125.32, 53.14, 51.41, 41.27, 39.60, 39.18, 39.00, 35.33, 28.93, 25.39. Anal. (C₂₀H₂₂O₂) C, H. **9b**: ¹H-NMR δ 7.77(m, 3H), 7.63 (bs, 1H), 7.44 (m, 2H), 7.34 (dd, 1H, *J* = 9, 2 Hz), 3.48 (s, 3H), 3.26 (ddd, 1H, *J* = 11, 11, 7 Hz), 2.58 (d, 1H, *J* = 11 Hz) 2.35-2.45 (m, 2H), 2.32 (ddd, 1H, *J* = 12, 7, 7 Hz), 2.05 (bd, 1H, *J* = 12 Hz), 1.96 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.52 (m, 1H), 1.40 (dd, 1H, *J* = 12, 12 Hz), 1.15 (ddd, 1H, *J* = 12, 4, 4 Hz). ¹³C-NMR δ 176.34, 142.24, 133.55, 132.32, 128.03, 127.71, 127.61, 126.35, 126.26, 125.90, 125.35, 56.10, 51.58, 39.24, 37.59, 37.25, 33.65, 33.08, 32.07, 30.09. Anal. (C₂₀H₂₂O₂) C, H.

2α-Carbomethoxy-3α-naphthyl-bicyclo(3.2.1)octane (**10b**).

Compound **5b** (200 mg, 0.68 mmol) was hydrogenated under pressure (50 psi) in the presence of Pd-C (10% w/w 118 mg) in methanol (40 mL) overnight. The resulting mixture was filtered through Celite and the methanol evaporated. The crude residue (180 mg) contained a mixture of products and was purified by gravity column chromatography on flash silica (eluent: 40 – 8-% toluene/hexanes) to afford 85 mg of a white solid. Recrystallization from ethanol gave analytically pure **10b** (70 mg), mp 91.1-91.3°C; ¹H-NMR δ 7.75 (m, 3H), 7.70 (bs, 1H), 7.40 (m, 3H), 3.35-3.45 (m, 2H), 3.36 (s, 3H), 2.70 (m, 1H), 2.40 (m, 1H), 2.29 (ddd, 1H, *J* = 12, 7, 7 Hz), 2.20 (ddd,

1H, $J = 12, 12, 2$ Hz), 1.89 (bd, 1H, $J = 12$ Hz), 1.50-1.80 (m, 3H), 1.45 (m, 1H), 1.35 (ddd, 1H, $J = 12, 4, 4$ Hz). ^{13}C -NMR δ 174.35, 141.37, 133.36, 131.88, 127.90, 127.45, 127.29, 126.87, 125.75, 125.72, 125.24, 52.55, 50.96, 38.60, 36.83, 34.85, 33.58, 33.16, 29.92, 28.29. Anal. ($\text{C}_{20}\text{H}_{22}\text{O}_2$) C, H.

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B. SYNTHESIS OF 3-ARY-8-OXABICYCLO (3.2.1)OCTANES.

Schemes 2 and 3 (Figures 3 and 4) show the synthesis of 3-ary-8-oxabicyclo (3.2.1)octanes.

10 **(1*R*,1*S*)-2-Carbomethoxy-3-(((trifluoromethyl)sulfonyl)oxy)-8-oxabicyclo(3.2.1)-2-octene (14).**

Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 45 mL) was added dropwise to 2-carbomethoxy-8-oxabicyclo(3.2.1) octanone, **13**²⁵ (7.12 g, 38.65 mmol) in THF (100 mL) at -70 °C under nitrogen. After stirring for 30 min, N-phenyltrifluoromethanesulfonimide (15.19 g, 42.52 mmol) was added as a solid at -70 °C. The reaction was allowed to warm to room temperature and was then stirred overnight. The volatiles were removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and brine (100 mL). The dried (MgSO_4) CH_2Cl_2 layer was concentrated to dryness on a rotary evaporator. The residue was purified by flash chromatography (eluent: 5%-10% EtOAc/hexanes) to afford 9.62 g (79%) of **14** as a pale yellow oil: ^1H -NMR (CDCl_3 , 100 MHz): δ 5.0-5.1 (m, 1H), 4.6-4.8 (m, 1H), 3.83 (s, 3H), 3.0 (dd, 1H, $J = 5, 8$ Hz), 1.7-2.35 (m, 5H).

25 **General Procedure for Synthesis of the 2-Octenes: (1*R*,1*S*)-2-Carbomethoxy-3-phenyl-8-oxabicyclo(3.2.1)-2-octene (15a).**

2-Carbomethoxy-3-(((trifluoromethyl)sulfonyl)oxy)-8-oxabicyclo(3.2.1)-2-octene, **14** (2.0 g, 6.32 mmol), phenyl boronic acid (1.02 g, 8.36 mmol), diethoxymethane (20 mL), LiCl (578 mg, 13.6 mmol), tris(dibenzylideneacetone) dipalladium(0) (247 mg, 0.25 mmol) and Na_2CO_3 (2 M solution, 6.1 mL) were combined and heated at reflux for 1 h. The mixture was cooled to room temperature,

filtered through Celite and washed with ether (100 mL). The mixture was basified with NH_4OH and washed with brine. The dried (MgSO_4) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 1.28 g (82%) of **15a** as a light brown viscous oil: R_f 0.26 (20% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.1-7.5 (m, 5H), 4.95-5.1 (m, 1H), 4.55-4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, $J = 5, 18$ Hz), 1.7-2.2 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{16}\text{O}_3$) C, H.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-fluorophenyl)-8-oxabicyclo(3.2.1)-2-octene (15b).

Compound **15b** was prepared from **14** with 4-fluorophenylboronic acid as described for **15a**. A light brown viscous oil was obtained (88%): R_f 0.19 (20% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.0-7.2 (m, 4H), 4.95-5.05 (m, 1H), 4.55-4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, $J = 5, 18$ Hz), 1.7-2.3 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{15}\text{O}_3\text{F}$) C, H.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-chlorophenyl)-8-oxabicyclo(3.2.1)-2-octene (15c).

Compound **15c** was prepared from **14** with 4-chlorophenylboronic acid as described for **15a**. A light brown viscous oil was obtained (92%): R_f 0.23 (20% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.0-7.4 (m, 4H), 4.95-5.1 (m, 1H), 4.55-4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, $J = 5, 18$ Hz), 1.7-2.2 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{15}\text{O}_3\text{Cl}$) C, H, Cl.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-bromophenyl)-8-oxabicyclo(3.2.1)-2-octene (15d).

Compound **15d** was prepared from **14** with 4-bromophenylboronic acid as described for **15a**. A clear viscous oil was obtained (41%): R_f 0.39 (20% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.48 (d, 2H, $J = 9$ Hz), 6.97 (d, 2H, 9 Hz), 4.95-5.1 (m, 1H), 4.5-4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, $J = 5, 18$ Hz), 1.65-2.4 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{15}\text{O}_3\text{Br}$) C, H, Br.

(1*R*,1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)-2-octene (15f).

Compound **15f** was prepared from **14** with 3,4-chlorophenylboronic acid as described for **15a**. A light brown viscous oil was obtained (97%): *R_f* 0.45 (30%

5 EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): δ 7.4 (d, 1H, *J* = 10 Hz), 7.23 (d, 1H, *J* = 2 Hz), 6.95 (dd, 1H, *J* = 2, 10 Hz), 4.95-5.1 (m, 1H), 4.55-4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, *J* = 5, 18 Hz), 1.6-2.3 (m, 5H). Anal. (C₁₅H₁₄O₃Cl₂) C, H, Cl.

(1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)-2-octene (15g).

10 Compound **15g** was prepared from (*1*R**)-**14** with 3,4-chlorophenylboronic acid as described for **15a**. A light brown viscous oil was obtained (94%): *R_f* 0.45 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): identical to **5f** above.

(1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)-2-octene (15h).

15 Compound **15h** was prepared from (*1*S**)-**14** with 3,4-chlorophenylboronic acid as described for **15a**. A clear viscous oil was obtained (80%): *R_f* 0.45 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): identical to **15f** above.

General Procedure for Synthesis of the Octanes: (1*R*,1*S*)-2β-Carbomethoxy-3β-phenyl-8-oxabicyclo(3.2.1)octane (16a) and (1*R*,1*S*)-2β-Carbomethoxy-3α-phenyl-8-oxabicyclo(3.2.1)octane (17a).

To 2-carbomethoxy-3-phenyl-8-oxabicyclo(3.2.1)-2-octene, **15a** (1.17 g, 4.8 mmol) in THF (10 mL) at -70 °C under N₂ was added SmI₂ (0.1 M in THF, 215 mL, 21.5 mmol). After the mixture was stirred for 30 min, MeOH (anhydrous, 25 mL) was added. The mixture was stirred at -70 °C for a further 2 h. The mixture was quenched with TFA (5 mL) and H₂O (100 mL). After warming to 0 °C, NH₄OH was added to attain pH 11 and the mixture was then stirred for 30 min. The mixture was filtered through Celite and washed with ether (400 mL) and then saturated with Na₂S₂O₃. The ether layer was washed with brine. The dried (MgSO₄) ether layer was concentrated to dryness. The isomers were separated by gravity column

chromatography (eluent: 10% EtOAc/hexanes) to afford 270 mg (23%) of **16a** as a white solid: mp 102.5-104 °C; R_f 0.30 (30% EtOAc/hexanes); and 789 mg (67%) of **17a** as a white solid: mp 96.5-98 °C; R_f 0.37 (30% EtOAc/hexanes); (**16a**): $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.25 (br s, 5H), 4.55-4.8 (m, 2H), 3.48 (s, 3H), 3.25 (ddd, 1H, J = 5, 5, 14 Hz), 2.6-3.0 (m, 2H), 1.5-2.3 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{18}\text{O}_3$) C, H. (**17a**): $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.25 (br s, 5H), 4.4-4.65 (m, 2H), 3.58 (s, 3H), 3.25 (ddd, 1H, J = 7, 11, 11 Hz), 2.52 (dd, 1H, J = 2, 11 Hz), 1.6-2.5 (m, 5H), 1.41 (ddd, 1H, J = 2, 11, 14 Hz). Anal. ($\text{C}_{15}\text{H}_{18}\text{O}_3$) C, H.

10 **(1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-fluorophenyl)-8-oxabicyclo(3.2.1)octane (16b) and (1*R*,1*S*)-2 β -Carbomethoxy-3 α -(4-fluorophenyl)-8-oxabicyclo (3.2.1)octane (17b).**

Compounds **16b** and **17b** were prepared from **15b** as described for compounds **16a** and **17a**. Compound **16b** was obtained (22%) as a white solid: mp 118-120.5 °C; R_f 0.27 (30% EtOAc/hexanes); and **17b** (62%) as a white solid: mp 58-60 °C; R_f 0.36 (30% EtOAc/hexanes). (**16b**): $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.15-7.25 (m, 2H), 6.9-7.0 (m, 2H), 4.6-4.7 (m, 2H), 3.48 (s, 3H), 3.17 (ddd, 1H, J = 5, 5, 13 Hz), 2.78 (d, 1H, J = 5 Hz), 2.73 (ddd, 1H, J = 4, 13, 13 Hz), 1.7-2.2 (m, 4H), 1.5-1.65 (m, 1H). Anal. ($\text{C}_{15}\text{H}_{17}\text{O}_3\text{F}$) C, H. (**17b**): $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.1-7.2 (m, 2H), 6.9-7.0 (m, 2H), 4.5-4.8 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, J = 7, 11, 11 Hz), 2.44 (dd, 1H, J = 2, 11 Hz), 2.38 (ddd, 1H, J = 7, 9, 13 Hz), 1.9-2.2 (m, 2H), 1.76 (ddd, 1H, J = 5, 9, 13 Hz), 1.6-1.7 (m, 1H), 1.32 (ddd, 1H, J = 2, 11, 13 Hz). Anal. ($\text{C}_{15}\text{H}_{17}\text{O}_3\text{F}$) C, H.

25 **(1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-chlorophenyl)-8-oxabicyclo(3.2.1)octane (16c) and (1*R*,1*S*)-2 β -Carbomethoxy-3 α -(4-chlorophenyl)-8-oxabicyclo (3.2.1) octane (17c).**

Compounds **16c** and **17c** were prepared from **15c** as described for compounds **16a** and **17a**. Compound **16c** was obtained (19%) as a white solid: mp 116-117 °C; R_f 0.27 (30% EtOAc/hexanes); and **17c** (51%) as a white solid: mp 89-90 °C; R_f 0.32

(30% EtOAc/hexanes). **(16c)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.1-7.4 (m, 4H), 4.55-4.8 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, $J = 5, 5, 12$ Hz), 2.55-2.95 (m, 2H), 1.5-2.3 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{17}\text{O}_3\text{Cl}$) C, H, Cl. **(17c)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.1-7.4 (m, 4H), 4.4-4.65 (m, 2H), 3.58 (s, 3H), 3.05-3.45 (m, 1H), 1.2-2.6 (m, 7H). Anal. ($\text{C}_{15}\text{H}_{17}\text{O}_3\text{Cl}$) C, H, Cl.

(1*R*,1*S*)-2 β -Carbomethoxy-3 α -(4-bromophenyl)-8-oxabicyclo(3.2.1)octane (16d) and (1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-bromophenyl)-8-oxabicyclo(3.2.1)octane (17d).

Compounds **16d** and **17d** were prepared from **15d** as described for compounds **16a** and **17a** except no TFA was used when quenching. Compound **16d** was obtained (47%) as a white solid: mp 113-115 $^\circ\text{C}$; R_f 0.29 (30% EtOAc/hexanes); and **17d** (32%) as a white solid: mp 96-98 $^\circ\text{C}$; R_f 0.38 (30% EtOAc/hexanes). **(16d)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.45 (d, 2H, $J = 9$ Hz), 7.15 (d, 2H, $J = 9$ Hz), 4.6-4.8 (m, 2H), 3.5 (s, 3H), 3.0-3.4 (m, 1H), 2.55-2.9 (m, 2H), 1.5-2.4 (m, 5H). Anal. $\text{C}_{15}\text{H}_{17}\text{O}_3\text{Br}$. **(17d)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.45 (d, 2H, $J = 10$ Hz), 7.1 (d, 2H, $J = 10$ Hz), 4.4-4.6 (m, 2H), 3.53 (s, 3H), 3.20 (ddd, 1H, $J = 6, 11, 11$ Hz), 1.6-2.6 (m, 6H), 1.35 (ddd, 1H, $J = 2, 11, 13$ Hz). Anal. ($\text{C}_{15}\text{H}_{17}\text{O}_3\text{Br}$) C, H, Br.

(1*R*,1*S*)-2 β -Carbomethoxy-3 β -(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1) octane (16f) and (1*R*,1*S*)-2 β -Carbomethoxy-3 α -(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)octane (17f).

Compounds **16f** and **17f** were prepared from **15f** as described for compounds **16a** and **7a**. Compound **16f** was obtained (14%) as a white solid: mp. 132-133.5 $^\circ\text{C}$; R_f 0.31 (30% EtOAc/hexanes); and **17f** (55%) as a white solid: mp. 88.5-90 $^\circ\text{C}$; R_f 0.33 (30% EtOAc/hexanes). **(6f)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.0-7.5 (m, 3H), 4.55-4.85 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, $J = 5, 5, 11$ Hz), 2.55-2.95 (m, 2H), 1.45-2.35 (m, 5H). Anal. ($\text{C}_{15}\text{H}_{16}\text{O}_3\text{Cl}_2$) C, H, Cl. **(17f)**: $^1\text{H-NMR}$ (CDCl_3 , 100 MHz): δ 7.0-7.5 (m, 3H), 4.4-4.65 (m, 2H), 3.60 (s, 3H), 3.20 (ddd, 1H, $J = 7, 11, 11$

Hz), 1.5-2.5 (m, 6H), 1.30 (ddd, 1H, J = 2, 11, 13 Hz). Anal. (C₁₅H₁₆O₃Cl₂) C, H, Cl.

(1*R*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1) octane (16g)

5 and

(1*R*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)octane (17g).

Compounds **16g** and **17g** were prepared from (*1*R**)- **15f** as described for compounds **16a** and **17a**. Compound **16g** was obtained (13%) as a white solid: mp 121-122 °C; *R_f* 0.31 (30% EtOAc/hexanes); and **17g** (45%) as a white solid: mp 103.5-104.5 °C; (α)_D²¹ = -79° (c = 1, MeOH); *R_f* 0.33 (30% EtOAc/hexanes). (**16g** and **17g**): ¹H-NMR (CDCl₃, 100 MHz): identical to **16f** and **17f** above. Anal. (C₁₅H₁₆O₃Cl₂) C, H, Cl.

(1*S*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1) octane (16h)

15 and **(1*S*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxabicyclo(3.2.1)octane (17h). C**

Compounds **16h** and **17h** were prepared from (*1*S**)- **15f** as described for compounds **16a** and **17a**. Compound **16h** was obtained (11%) as a white solid: mp 121-122 °C; *R_f* 0.31 (30% EtOAc/hexanes); and **17h** (45%) as a white solid: mp 103-104 °C; (α)_D²¹ = +76° (c = 1, MeOH); *R_f* 0.33 (30% EtOAc/hexanes). (**16h** and **17h**): ¹H-NMR (CDCl₃, 100 MHz): identical to **16f** and **17f** above. Anal. (C₁₅H₁₆O₃Cl₂) C, H, Cl.

Synthesis of (1*R*,1*S*)-2-Carbomethoxy-3-(4-iodophenyl)-8-oxabicyclo(3.2.1)-2-octene, 15e: (1*R*,1*S*)-2-Carbomethoxy-3-(4-tributylstannylphenyl)-8-oxabicyclo(3.2.1)-2-octene.

2-Carbomethoxy-3-(4-bromophenyl)-8-oxabicyclo{3.2.1)-2-octene, **15d** (200 mg, 0.62 mmol), tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.011 mmol) and bis(tributyltin) (0.74 mL, 1.46 mmol) in toluene (4 mL) were degassed by bubbling N₂

through the solution for 10 min. The mixture was then heated at reflux for 6 h. CH₂Cl₂ (10 mL) was added and the mixture was filtered through Celite. The filtrate was concentrated to dryness. The residue was purified sequentially by flash chromatography (eluent: 30% EtOAc/hexanes) and preparative TLC (eluent: 5%-10% EtOAc/hexanes) to afford 206 mg (62%) of the title compound as a clear viscous oil: *R_f* 0.31 (59% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): δ 7.43 (d, 2H, *J* = 7 Hz), 7.05 (d, 2H, *J* = 7 Hz), 4.95-5.1 (m, 1H), 4.55-4.75 (m, 1H), 3.50 (s, 3H), 2.95 (dd, 1H, *J* = 5, 18 Hz), 0.7-2.3 (m, 32H).

10 **(1*R*,1*S*)-2-Carbomethoxy-3-(4-iodophenyl)-8-oxabicyclo(3.2.1)-2-octene (15e).**

2-Carbomethoxy-3-(4-tributylstannylphenyl)-8-oxabicyclo(3.2.1)-2-octene (206 mg, 0.39 mmol) from above, in THF (anhydrous, 5mL) was degassed by bubbling N₂ for 10 min. N-Iodosuccinimide (96 mg, 0.43 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and concentrated to dryness.

15 The residue was dissolved in ether (10 mL), washed with saturated NaHCO₃ and brine. The dried (MgSO₄) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) and preparative TLC (eluent: 30% EtOAc/hexanes) to afford 128 mg (90%) of **15e** as a pale yellow viscous oil: *R_f* 0.49 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): δ 7.68 (d, 2H, *J* = 10 Hz), 6.85 (d, 2H, *J* = 10 Hz), 4.95-5.05 (m, 1H), 4.55-4.75 (m, 1H), 3.54 (s, 3H), 2.95 (dd, 1H, *J* = 5, 18 Hz), 1.55-2.40 (m, 5H). Anal. (C₁₅H₁₅O₃I) C, H, I.

25 **Synthesis of (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-iodophenyl)-8-oxabicyclo(3.2.1)octane (17e): (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-tributylstannylphenyl)-8-oxabicyclo(3.2.1) octane.**

The title compound was prepared from **17d**, as described above for stannylation of **15d**. A clear viscous oil (41%) was obtained: *R_f* 0.48 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): δ 7.4 (d, 2H, *J* = 7 Hz), 7.2 (d, 2H, *J* = 7 Hz), 4.4-4.6 (m, 2H), 3.60 (s, 3H), 3.25 (ddd, 1H, *J* = 6, 10, 10 Hz), 0.7-2.65 (m, 30 34H).

(1*R*,1*S*)-2 β -Carbomethoxy-3 α -(4-iodophenyl)-8-oxabicyclo(3.2.1)octane (17e).

Compound **17e** was prepared from the above stannyl compound as described for **15e** from 2 β -carbomethoxy-3 α -(4-tributylstannylphenyl)-8-oxabicyclo(3.2.1)

5 octane (85%). A white solid was obtained: mp 124-126 °C; *R*_f0.36 (30%

EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz): δ 7.6 (d, 2H, *J* = 9 Hz), 6.97 (d, 2H, *J* = 9 Hz), 4.35-4.65 (m, 2H), 3.6 (s, 3H), 3.2 (ddd, 1H, *J* = 6, 11, 11 Hz), 1.5-2.6 (m, 6H), 1.35 (ddd, 1H, *J* = 2, 11, 13 Hz). Anal. (C₁₅H₁₇O₃I) C, H, I.

10 **Synthesis of (1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-iodophenyl)-8-oxabicyclo(3.2.1)octane (16e): (1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-nitrophenyl)-8-oxabicyclo(3.2.1)octane.**

To 2 β -carbomethoxy-3 β -phenyl-8-oxabicyclo(3.2.1)octane, **16a** (112 mg, 0.45 mmol) in CH₃CN (anhydrous, 5 mL) at -5 °C was added NO₂BF₄ (83 mg, 0.63
15 mmol). The reaction mixture was stirred at -5 °C for 3 h. A small amount of ice was added and the mixture was stirred at -25 °C for 15 min. The CH₃CN was removed, the melted ice was extracted with ether. The combined ether extract and CH₃CN solution were concentrated to dryness. The residue was dissolved in ether (50 mL), washed with saturated NaHCO₃ and brine. The dried (MgSO₄) ether layer was concentrated to
20 dryness. The residue was purified by flash chromatography (eluent: 10%-20% EtOAc/hexanes) to afford 75.6 mg (57%) of the title 4-nitro-compound: *R*_f0.19 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃, 100 MHz) δ 8.2 (d, 2H, *J* = 10 Hz), 7.42 (d, 2H, *J* = 10 Hz), 4.6-4.85 (m, 2H), 3.54 (s, 3H), 3.15-3.45 (m, 1H), 2.6-3.0 (m, 2H), 1.7-2.4 (m, 5H).

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(1*R*,1*S*)-2 β -Carbomethoxy-3 β -(4-aminophenyl)-8-oxabicyclo(3.2.1)octane.

2 β -Carbomethoxy-3 β -(4-nitrophenyl)-8-oxabicyclo(3.2.1)octane (75.6 mg, 0.026 mmol) in MeOH (20 mL) was hydrogenated overnight at room temperature using Raney Ni (50%) as catalyst. The reaction mixture was filtered through Celite,
30 washed with MeOH and concentrated to dryness. The residue was purified by flash

chromatography (eluent: 20%-30% EtOAc/hexanes) to afford 43 mg (75%) of the title 4-amino-compound: R_f 0.22 (50% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ 7.05 (d, 2H, $J = 9$ Hz), 6.62 (d, 2H, $J = 9$ Hz), 4.55-4.7 (m, 2H), 3.58 (br s, 2H), 3.50 (s, 3H), 3.0-3.3 (m, 1H), 2.5-2.9 (m, 2H), 1.4-2.3 (m, 5H).

5

(1*R*,1*S*)-2- β -Carbomethoxy-3- β -(4-iodophenyl)-8-oxabicyclo(3.2.1)octane (16e).

To 2- β -carbomethoxy-3- β -(4-aminophenyl)-8-oxabicyclo(3.2.1)octane (26 mg, 0.099 mmol) in CH_2I_2 (2 mL) under N_2 was added isoamyl nitrite (0.17 mL, 0.126 mmol). The reaction mixture was stirred at room temperature for 1 h then at 55 °C for 3 h. CH_2I_2 was removed under reduced pressure. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 15 mg (60%) of **6e** as a white solid: mp 119-120.5 °C; R_f 0.25 (30% EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ 7.65 (d, 2H, $J = 9$ Hz), 7.00 (d, 2H, $J = 9$ Hz), 4.6-4.8 (m, 2H), 3.52 (s, 3H), 3.05-3.3 (m, 1H), 2.55-2.9 (m, 2H), 1.5-2.3 (m, 5H).

15

(1*R*,1*S*)-2- β -Carbomethoxy-3-(4-acetylphenyl)-8-oxabicyclo(3.2.1)-2-octene (15i).

Compound **15i** was prepared from **14** with 4-acetylphenylboronic acid as described for **15a**. A light yellow solid was obtained (64%): m.p. 120-121 °C; R_f 0.22 (30% EtOAc/hexanes); $^1\text{HNMR}$ δ (CDCl_3 , 300 MHz): 7.93 (d, 2H), 7.20 (d, 2H), 5.02 (d, 1H), 4.66 (t, 1H), 3.52 (s, 3H), 2.96 (dd, 1H), 2.60 (s, 3H), 2.29-2.06 (m, 4H), 1.83-1.73 (m, 1H). Anal. ($\text{C}_{17}\text{H}_{18}\text{O}_4$) C, H.

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(1*R*,1*S*)-2- β -Carbomethoxy-3-(4-isopropylphenyl)-8-oxabicyclo(3.2.1)-2-octene (15j).

Compound **15j** was prepared from **14** with 4-isopropylphenylboronic acid as described for **15a**. A light yellow oil was obtained (80%): R_f 0.46 (30% EtOAc/hexanes); $^1\text{HNMR}$ (CDCl_3 , 300 MHz): δ 7.17 (d, 2H), 7.04 (d, 2H), 4.99 (d, 1H), 4.63 (t, 1H), 3.51 (s, 3H), 3.02-2.85 (m, 2H), 2.26-2.04 (m, 4H), 1.83-1.73 (m, 1H), 1.23 (d, 6H). Anal. ($\text{C}_{18}\text{H}_{22}\text{O}_3$) C, H.

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(1*R*,1*S*)-2-Carbomethoxy-3-(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)-2-octene (15k).

Compound **15k** was prepared from **15i** as follows:

Methyltriphenylphosphonium bromide (0.35 g, 1.0 mmol) was dissolved in anhydrous THF (5 mL) under N₂ and cooled to -78 °C. *n*-Butyllithium (0.46 mL, 2.5 M in THF, 1.15 mmol) was added slowly. This mixture was stirred for 20 min at -78 °C. (1*R*, 1*S*)-2-Carbomethoxy-3-(4-acetylphenyl)-8-oxabicyclo(3.2.1)-2-octene (**5i**, 0.22 g, 0.77 mmol) in THF (2 mL) cooled at 0 °C was added via canula. The resulting mixture was allowed to warm up to room temperature and was stirred at room temperature for 23 h. The reaction was quenched by water (25 mL). This was extracted with ether (40 mL). The ether extract was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by flash column chromatography to afford 118 mg white solid (54%): R_f 0.45 (30% EtOAc/hexanes); ¹HNMR (CDCl₃, 300 MHz): δ 7.43 (d, 2H), 7.09 (d, 2H), 5.40 (s, 1H), 5.09 (s, 1H), 5.01 (d, 1H), 4.65 (t, 1H), 3.54 (s, 3H), 2.96 (dd, 1H), 2.26-2.05 (m, 7H), 1.83-1.74 (m, 1H). Anal. (C₁₈H₂₀O₃) C, H.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-propynylphenyl)-8-oxabicyclo(3.2.1)-2-octene (15l).

Compound **15l** was prepared from **15m** and propynyltributyltin as follows:

(1*R*, 1*S*)-2-Carbomethoxy-3-(4-bromophenyl)-8-oxabicyclo(3.2.1)-2-octene (**15m**, 0.5 g, 1.55 mmol) and propynyltributyltin (0.62 g, 1.88 mmol) were combined in anhydrous toluene (40 mL) and N₂ was bubbled through for 10 min. This solution was added via canula to a flask charged with tetrakis(triphenylphosphine)palladium(0) (0.18 g, 0.16 mmol) protected under N₂. The resulting solution was heated at reflux for 5 h. The reaction solution was cooled to room temperature and diluted with ether (50 mL). This was filtered through celite. The filtrate was evaporated to dryness. The residue was purified by flash column chromatography to afford 181 mg off-white solid (42%). Recrystallization of this slightly impure product (99 mg) from EtOAc/hexanes afforded a pure product (white solid, 62 mg): m.p. 93.5-94 °C; R_f 0.40 (30% EtOAc/hexanes); ¹HNMR (CDCl₃, 300 MHz): δ 7.33 (d, 2H), 7.02 (d, 2H), 4.99 (d,

1H), 4.63 (t, 1H), 3.48 (s, 3H), 2.96 (dd, 1H), 2.25-2.06 (m, 4H), 2.04 (s, 3H), 1.82-1.71 (m, 1H). Anal. (C₁₈H₁₈O₃) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-propynylphenyl)-8-oxabicyclo(3.2.1)octane (16l)
5 **and (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-propynylphenyl)-8-oxabicyclo(3.2.1)octane (17l).**

Compounds **16l** and **17l** were prepared from **15l** as described for compounds **16a** and **17a**. Compound **16l** was obtained (52%) as a white solid: m.p. 142-143 °C; R_f 0.27 (30% EtOAc/hexanes); and compound **17l** (13%) as a white solid: m.p. 96.5-97.5 °C; R_f 0.40 (30% EtOAc/hexanes). **(16l)**: ¹H NMR (CDCl₃, 300 MHz): δ 7.30 (d, 2H), 7.15 (d, 2H), 4.70-4.62 (m, 2H), 3.48 (s, 3H), 3.24-3.13 (m, 1H), 2.84-2.70 (m, 2H), 2.20-1.74 (m, 4H), 2.03 (s, 3H), 1.64-1.57 (m, 1H). Anal. (C₁₈H₂₀O₃) C, H.
(17l): ¹H NMR (CDCl₃, 300 MHz): δ 7.30 (d, 2H), 7.13 (d, 2H), 4.54-4.42 (m, 2H), 3.56 (s, 3H), 3.32-3.16 (m, 1H), 2.50 (d, 1H), 2.45-2.32 (m, 1H), 2.18-1.92 (m, 2H), 2.03 (s, 3H), 1.80-1.58 (m, 2H), 1.45-1.31 (m, 1H). Anal. (C₁₈H₂₀O₃) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-isopropylphenyl)-8-oxabicyclo(3.2.1)octane (16j)
and **(1*R*,1*S*)-2β-Carbomethoxy-3α-(4-isopropylphenyl)-8-oxabicyclo(3.2.1)octane (17j).**

Compounds **16j** and **17j** were prepared from **15j** as described for compounds **16a** and **17a**. Compound **16j** was obtained (45%) as a light yellow oil: R_f 0.25 (30% EtOAc/hexanes); and compound **17j** (8.5%) as a light yellow oil: R_f 0.40 (30% EtOAc/hexanes). **(16j)**: ¹H NMR (CDCl₃, 300 MHz): δ 7.18-7.15 (m, 4H), 4.70-4.62 (m, 2H), 3.49 (s, 3H), 3.23-3.14 (m, 1H), 2.91-2.72 (m, 3H), 2.20-1.74 (m, 4H), 1.64-1.57 (m, 1H), 1.22 (d, 6H). Anal. (C₁₈H₂₄O₃) C, H. **(17j)**: ¹H NMR (CDCl₃, 300 MHz): δ 7.13 (s, 4H), 4.54-4.46 (m, 2H), 3.58 (s, 3H), 3.29-3.19 (m, 1H), 2.91-2.80 (m, 1H), 2.55-2.51 (m, 1H), 2.47-2.35 (m, 1H), 2.19-1.61 (m, 4H), 1.46-1.37 (m, 1H), 1.23 (d, 6H). Anal. (C₁₈H₂₄O₃) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)octane (16k) and (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-isopropenylphenyl)-8-oxabicyclo(3.2.1)octane (17k).

Compounds **16k** and **17k** were prepared from **15k** as described for compounds **16a** and **17a**. Compound **16k** was obtained (54%) as a light yellow solid: m.p. 72.3-73.3 °C; *R*_f 0.31 (30% EtOAc/hexanes); and compound **17k** (24%) as a off-white solid: m.p. 87-88 °C; *R*_f 0.40 (30% EtOAc/hexanes). (**16k**): ¹H-NMR (CDCl₃, 300 MHz): δ 7.40 (d, 2H), 7.21 (d, 2H), 5.35 (s, 1H), 5.04 (s, 1H), 4.70-4.62 (m, 2H), 3.51 (s, 3H), 3.26-3.17 (m, 1H), 2.89-2.73 (m, 2H), 2.22-1.77 (m, 4H), 2.13 (s, 3H), 1.69-1.60 (m, 1H). Anal. (C₁₈H₂₂O₃) C, H. (**17k**): ¹H-NMR (CDCl₃, 300 MHz): δ 7.40 (d, 2H), 7.19 (s, 2H), 5.35 (s, 1H), 5.05 (s, 1H), 4.56-4.47 (m, 2H), 3.60 (s, 3H), 3.33-3.22 (m, 1H), 2.54 (dd, 1H), 2.46-2.37 (m, 1H), 2.22-1.94 (m, 2H), 2.13 (s, 3H), 1.83-1.58 (m, 2H), 1.47-1.38 (m, 1H). Anal. (C₁₈H₂₂O₃) C, H.

(1*R*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octa-2-ene-3-(1'*S*)-camphanate ((1*R*,1'*S*)- **19).**

(1*R*,1*S*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octan-3-one, **13** (7.4 g, 40.1 mmol) was dissolved in anhydrous THF (200 mL) and cooled to -78 °C. To this solution was added butyl lithium (17.6 mL of a 2.5 M solution, 44.1 mmol); the color changed to yellow orange. After 15 min. at -78 °C (*S*)-(-)-camphanic chloride (9.6 g, 44.1 mmol) was added in one portion and then the cooling bath was removed. After 5 min. saturated Na₂CO₃ was added (300 mL) and ether (300 mL). The layers were separated and the ether phase washed with brine (100 mL) and dried (MgSO₄). Filtration followed by evaporation gave the crude reaction product (14 g). Purification by column chromatography (SiO₂, 400 g, eluent: 30% ethyl acetate in hexanes) gave the diastereomeric mixture, **18** (8.29 g, 57%). ¹H-NMR of the diagnostic camphanate methyls were δ (1*S*,1'*S*) 1.04 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H); (1*R*,1'*S*) 1.06 (s, 3H) 1.14 (s, 6H). This mixture, **18**, was recrystallized eight times from methylene chloride/hexanes and gave white crystals of the pure title compound (1*R*,1'*S*)- **19** (2.25 g, 54%): mp 168.9-169 °C; *R*_f 0.25 (30% EtOAc/hexanes); ¹H-NMR (CDCl₃,

100 MHz) δ 5.04 (br. s, 1H), 5.55-5.75 (m, 1H), 3.71 (s, 3H), 2.90 (dd, $J = 5, 18$ Hz), 1.6-2.7 (m, 9 H), 1.14 (s, 6 H), 1.06 (s, 3H). Anal. ($C_{19}H_{24}O_7$) C, H.

(*IS*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octa-2-ene-3-(*I'R*)-camphanate

5 **((*IS,I'R*)- 19).**

The title compound was obtained as follows: Hydrolysis (LiOH) of the residual mother liquor obtained from recrystallization of (*IR,I'S*)- 19 above gave an enriched mixture (*IS*: 60% ee) of (*IR,IS*)-2-carbomethoxy-8-oxabicyclo(3.2.1)octan-3-one, 13. Reaction with (*R*)-(+)-camphanic chloride then gave the camphanate (2.79 g, 72%).

10 Recrystallization twice from methylene chloride/hexanes gave 1.29 g (92%) of the pure (*IS,I'R*)- 19 diastereomer. This had the same physical and chemical properties as the above ester (*IR,I'S*)- 19. Anal. ($C_{19}H_{24}O_7$) C, H.

(*IR*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octan-3-one ((*IR*)- 13).

15 (*IR*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octa-2-ene-3-(*S*)-camphanate, (*IR,I'S*)- 19 (1.76 g, 4.8 mmol) was dissolved in THF (15 mL) and then methanol (5 mL) and water (5 mL) were added. The resulting solution was cooled in an ice bath and lithium hydroxide (325 mg, 7.7 mmol) was added in one portion. After 20 min no (*IR,I'S*)- 19 remained. The solution was neutralized with 1 M hydrochloric acid. Ether
20 (200 mL) was then added and the ethereal solution was washed with brine and dried ($MgSO_4$). Evaporation gave 1.38 g of the crude reaction product. This was chromatographed (SiO_2 , 50 g, eluent: 20% ether in hexanes) to yield 833 mg (94%) of the pure title compound. 1H -NMR and TLC were identical with the racemic ketone 13. Under chiral HPLC conditions (Chiralcel OC column, eluent: 10% isopropanol in
25 hexanes 1 mL/min.) t_R (*IS*)- 13 = 6.99 min (1.78 %); t_R (*IR*)- 13 = 10.92 min (98.21 %, ee = 96.4%).

(*IS*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octan-3-one ((*IS*)- 13).

The title compound was obtained upon LiOH hydrolysis, as described above,
30 from (*IS*)-2-Carbomethoxy-8-oxabicyclo(3.2.1)octa-2-ene-3-(*I'R*)-camphanate: 0.78 g, 86%. 1H -NMR and TLC were identical with the racemic ketone 13. Under chiral

HPLC conditions (Chiralcel OC column, eluent: 10% isopropanol in hexanes, 1 mL/min) t_R (*IS*)- **13** = 6.87 (100 %, ee > 98%); t_R (*IR*)- **13** = not present.

PHARMACOLOGICAL AND BIOLOGICAL DATA

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EXAMPLE 1: Stable Expression of SERT in HEK-293 cells

The human serotonin transporter vector construct was transfected as a lipid suspension with Lipofectamine (Life Technologies, Inc., Gaithersburg, MD) into human embryonic kidney cells (HEK-293, American Type Culture Collection, Rockville, MD). Cells were plated 24 hours before transfection in Dulbecco's Modified Eagle growth medium supplemented with 10% fetal bovine serum, 100 U/ml penicillin and 100 µg/ml streptomycin, 1% non-essential amino acids (Gibco-BRL, Grand Island, NY) in 100 mm Falcon tissue culture dishes (VWR, S. Plainfield, NJ). The human serotonin transporter cDNA (courtesy of Dr. R.D. Blakely, Vanderbilt University, TN) was subcloned into (-)pcDNA3.1 (Invitrogen, San Diego, CA), which contained an antibiotic resistance gene. The cDNA expression vector construct encoding SERT (10 µg) was diluted in 1 ml of serum free medium (Opti-Mem I, Life Technologies, Inc. Rockville, MD). The lipofectamine reagent (30 µl) was diluted in 1 ml of serum free medium separately from the DNA to avoid precipitation. The combined solution was added to 8 ml of serum free medium and incubated for 30 min to allow formation of DNA-liposome complexes. At about 50% confluence, the cells were incubated for 5 hours with the transfection mixture and the medium was changed. Cells were incubated at 37°C in a humidified 5% CO₂ incubator for 72 hours and then selected for more than two weeks with 600 µg/ml Geneticin (G418, Life Technologies, Inc., Rockville, MD). The resistant cells were divided and individual foci were harvested using cloning rings (Bel-Art Products, Pequannock, NJ) and trypsin (Life Technologies, Inc., Rockville, MD). Multiple cell lines were tested for (³H)serotonin transport. The clone that displayed the highest serotonin transport was chosen for this study and is referred to as SERT. Thereafter, the selecting antibiotic geneticin sulfate (250 µg/ml) was used continuously for culture of cells expressing the serotonin transporter.

(³H)Serotonin Transport: Cell preparation

Low passage number cells (<25 passage cycle) at 80-90% confluency in 145 mm dishes (Greiner Mediatech, Bel Air, MD) were used to measure (³H)serotonin transport. The medium was removed by aspiration, and cells were washed with Tris-Hepes buffer, pH 7.4 at 25°C (Tris base: 5 mM; Hepes: 8.5 mM; NaCl: 120 mM; KCl: 5.4 mM; CaCl₂: 1.2 mM; MgSO₄: 1.2 mM; and glucose: 10 mM), supplemented with pargyline (100 µM). The cells were harvested, centrifuged at 1000g for 5 min, washed twice with the Tris-Hepes buffer and diluted to 250,000 and 1,250,000 cells/ml for stable and transient cell lines, respectively.

EXAMPLE 2: (³H)Serotonin transport: Pharmacology

The whole-cell suspension (0.2 ml; 5-16 µg of protein) was pre-incubated with various dilutions of each drug (0.2 ml; 10⁻¹² to 10⁻⁵M) for 15 min. Compounds to be tested were dissolved in ethanol (50 µl), hydrochloric acid (10 µl; 2N) and water to achieve a concentration of 1 mM. Subsequent dilutions were made directly in assay buffer. Non-amines were dissolved in 30% to 50% ethanol and buffer to achieve a concentration of 1 mM. The first dilution used (10⁻⁵ M) contained less than 1.75% ethanol. (³H)Serotonin transport was initiated by the addition of (³H)serotonin (0.2 ml) diluted with unlabeled serotonin to yield a final serotonin concentration of 20 nM.

Transport proceeded for 10 min at 25°C and was terminated as previously described or by centrifugation of the cells. Nonspecific transport was defined as transport in the presence of 10 µM fluoxetine, and these data were subtracted from total counts to yield specific accumulation of (³H)serotonin. Each concentration of drug was assayed in triplicate and each value is the mean ± S.E. of 2-5 independent experiments. Protein concentrations were determined by Bradford assay (Bio-Rad, Richmond, CA).

EXAMPLE 3: Non-amine affinity and transporter selectivity in primate striatum

Initial screening procedures for non-amines were conducted in primate striatum, a standard source of brain transporters for drug screening and for generating structure-activity relationships for this series (Table 1). (³H)Citalopram binding

studies were conducted with monkey brain tissue (4 mg/ml). Various dilution of drugs (0.2 ml; 10^{-12} to 10^{-3} M) were incubated with 1 nM (3 H)citalopram (0.2 ml; ≈ 80 Ci/mmol; DuPont-NEN, Boston, MA) for 2 hours, at 4°C. The binding experiments were terminated by rapid filtration and radioactivity measured as described above.

5 Nonspecific binding was defined by 10 μ M fluoxetine, and these data were subtracted from total counts to yield specific (3 H)citalopram binding. The experiments were performed in triplicate and each value is the mean \pm S.E. of 2-5 independent experiments. Analysis of (3 H)citalopram competition assays was performed with EBDA and LIGAND computer programs (Elsevier-Biosoft, Cambridge, U.K.).

10 Table 1 shows affinities of amines (*O*-401, *O*-1228, *O*-1229) and non-amines to compete with a selective high affinity serotonin transporter ligand, (3 H)citalopram, and with a selective high affinity dopamine transporter ligand, (3 H)CFT, in monkey striatum homogenates. Competition assays were performed with (3 H)citalopram (1 nM, SERT) or with (3 H)CFT (1 nM, DAT) and 8-12 concentrations of tested non-
15 amines, each conducted in triplicate as described in Materials and Methods. Values were determined by fitting data to the equation for competitive binding with EBDA computer program. Data represent the mean \pm S.D. of two or more experiments.

Table 1.

Ligand	Serotonin transporter (SERT) IC ₅₀ (nM)	Dopamine transporter (DAT) IC ₅₀ (nM)	SERT/DAT Selectivity
O-401	2.47 \pm 0.14	1.09 \pm 0.02	0.4
O-1229	2.19 \pm 0.18	0.49 \pm 0.04	0.2
O-1072	4.66 \pm 1.24	3.88 \pm 0.93	0.8
O-1228	5.95 \pm 1.37	0.57 \pm 0.34	0.1
(R)O-1809^a	10.2 \pm 2.1	1,010 \pm 246	99
(RS)O-1739	19.8 \pm 0.75	1,020 \pm 42	52
O-1391	33.9 \pm 1.85	13.5 \pm 0.9	0.4
O-1577	72.4 ^b	545 \pm 76	8
O-1669	72.5 \pm 12.6	27.1 \pm 0.1	0.4
O-1670	77.7 \pm 13.5	21.2 \pm 4.1	0.3
O-1585	152 \pm 26.5	446 \pm 94	3
O-1738	158 \pm 23	912 \pm 100	6

^aO-1809 is the active enantiomer of O-1739

^b_{n=1}

Non-amines competed with (³H)citalopram binding sites with affinities (range: 4.66 – 158 nM, Table 1), comparable to values for conventional amine nitrogen-containing antidepressants. Some compounds, including the 2β,3β dichlorophenyl series, were relatively non-selective for the serotonin over the dopamine transporter (O-1072, O-1391, O-1669, O-1670) whereas others were 52-, 99-fold (O-1809, O-1739) or moderately selective (O-1738, O-1585). Within the dichloro series (Fig. 1), O-1072, the oxa analog of O-401 retained high affinity for the serotonin (4.66 ± 1.24 nM) and dopamine transporters (3.88 ± 0.93 nM) compared with the progenitor amine O-401 (Table 1). Substitution of the 8-oxa with an 8-carba (O-1391) reduced potency for the SERT by 7-fold to 33.9 ± 1.85 nM. Nevertheless, the results indicate that putative aza-driven ionic bonding or oxa-driven hydrogen bonding are not necessary for high affinity binding to the serotonin transporter.

Among the most potent novel compounds tested were the naphthyl monoamines (O-1228, O-1229; 5.95 ± 1.37 and 2.19 ± 0.18 nM, respectively) but the corresponding carba-based non-amines O-1669 and O-1670 displayed lower affinities (72.5 ± 12.6; 77.7 ± 13.5 nM) than the parent monoamines. The 4-isopropenylphenyl non-amines were potent ((*R*)-O-1809: 10.2 ± 2.1 nM; (*RS*)-O-1739: 19.8 ± 0.75) and selective for the serotonin over the dopamine transporter. In contrast, the oxa diastereoisomeric propynyl pair O-1577 and O-1585 displayed modest affinity and selectivity for the serotonin over the dopamine transporter, lower than the corresponding dichloroaryl or 4'-isopropenylphenyl analogs. With the exception of the highly lipophilic non-amines O-1669 and O-1670, the affinities of compounds for inhibiting (³H)citalopram labeled sites in monkey striatum and in HEK cells transfected with the human hSERT were similar (Tables 1, 2).

Table 2 shows affinities of novel amines and non-amines at (³H)citalopram binding sites and (³H)serotonin transport in HEK-293 cells stably or transiently transfected with the human SERT. Non-amines are listed in accordance with their rank order of potency. Competition assays were performed with (³H)citalopram (1 nM) or with (³H)serotonin (20 nM) and 8-12 concentrations of tested non-amines, each conducted in triplicate as described above. Values were determined by fitting data to

the equation for competitive binding with EBDA computer program. Data represent the mean \pm S.E.M. of n independent experiments and are expressed as K_i values ($K_i = IC_{50}/(1+c/K_d \text{ or } K_m)$).

5 Table 2.

	⁽³⁾ H)citalopram binding	⁽³⁾ H)serotonin transport
Ligand	K_i (nM)	K_i (nM)
O-1229	1.42 \pm 0.78	0.14 \pm 0.07
O-1228	3.26 \pm 0.26	4.57 \pm 0.37
O-1809	9.6 \pm 1.3	16 \pm 4
O-1391	10.0 \pm 4.30	11.1 \pm 7.44
O-1739	17.7 \pm 6.3	33 \pm 2
O-1577	32.6 \pm 7.88	63.0 \pm 16.8
O-1585	76.1 \pm 10.5	56.7 \pm 10.4
O-1738	218 \pm 45.1	376 \pm 74
O-1669	289 \pm 150	28 \pm 2
O-1670	303 \pm 8.7	425 \pm 332

To determine the effects of non-amines and monoamines on ⁽³⁾H)serotonin transport, we initially characterized ⁽³⁾H)serotonin transport in hSERT cells with clinically relevant antidepressants (see above). Compounds that inhibited ⁽³⁾H)serotonin transport produced monophasic inhibition curves with Hill coefficients close to unity (data not shown). Correlation analysis of the potencies of amines for inhibiting ⁽³⁾H)serotonin transport and competing with ⁽³⁾H)citalopram binding sites yielded a low and insignificant Pearson correlation coefficient (r^2 : 0.63; p : 0.21). This poor correlation was attributable to the 2-17 fold higher affinities of antidepressant drugs and phenyltropane analogs for ⁽³⁾H)citalopram binding sites compared with their potencies for inhibiting ⁽³⁾H)serotonin transport (data not shown).

In hSERT cells, non-amine affinities for ⁽³⁾H)citalopram binding sites and ⁽³⁾H)serotonin transport were measured and compared with conventional amine

antidepressants. In these experiments the density of (³H)citalopram binding sites, B_{max} ranged from 1419 to 2800 fmol/mg of protein (data not shown). Non-amines were selected on the basis of several addressable comparisons, including affinity, enantioselectivity, serotonin: dopamine transporter selectivity and amines (aza) vs oxa or carba non-amines (Fig. 1).

Carba or oxa non-amines inhibited (³H)serotonin transport into HEK-293 cells stably expressing the hSERT in a concentration-dependent and saturable manner. The most potent non-amines, O-1391, O-1072, O-1809, blocked serotonin transport in the 10–20 nM range (Table 2).

The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements of this invention and still be within the scope and spirit of this invention as set forth in the following claims.

All references cited are incorporated herein in their entirety by reference.